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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,045	SANTI ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to a previous Office action, a written restriction requirement (Paper No. 6, mailed on September 19, 2002), Applicants filed an election received on October 28, 2002 (Paper No. 7). Claims 1-16 are pending in the instant Office action.

Election

2. Applicants' election without traverse of Group I, Claims 1-11, in Paper No. 7 is acknowledged. Claims 12-16 are withdrawn from further consideration as non-elected inventions. Claims 1-11 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/220,651 filed on July 25, 2000 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statements filed on October 28, 2002 (Paper No. 8) and October 30, 2002 (Paper No. 9) have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Compliance with the Sequence Rules

5. By virtue of the filing on May 16, 2003 (Paper No. 12), the instant application now fully complies with the sequence rules.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Fermentation Process for Desoxyepothilones---

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of exemplary host cells for the claimed methods (*Sorangium cellulosum*), epothilone epoxidase inhibitors - particularly metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone), and methods involving inactivation of the epoK gene in the polyketide synthase gene cluster producing epothilone so that the Abstract describes the disclosed subject matter and not just the examined claims.

8. The specification is objected to for the following discrepancies:

a) On page 5, line 27, the reference to 09/443,501 must be updated to USPN 6,303,342.

b) On page 8, the Table at the bottom has bad margins such that "ACP" (see line 26) is inappropriately in the gene column.

c) On pages 33-35, Example 4 is disclosed and includes data on metyrapone included in Figure 1; other data included in Figure 1 is not described experimentally and is, thus, confusing.

Clarification and/or correction are required.

Claim Objections

9. Claim 10 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. All the compounds listed in Claim 10 are not within the generic formula presented in Claim 9 due to the methoxy group depicted (instead of an ether as found in all the species of Claim 10). See pages 22-29 for structures of the species in Claim 10.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-4 and 6-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "epothilone producing microorganism" is unclear. The specification only refers to *Sorangium cellulosum* microorganisms that naturally produce epothilone by virtue of the epothilone polyketide synthase gene cluster. Is this term limited to *S. cellulosum*? Is this term limited to any microorganism that contains and effectively expresses the epothilone PKS gene cluster to produce an epothilone PKS that biosynthesizes epothilone? The limited description in the specification renders the metes and bounds of this term confusing. Clarification is required.

11. Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**an** epothilone epoxidase" (emphasis added) is unclear based on the disclosure. In the art, a single epothilone PKS gene cluster is known; it is from *S. cellulosum* and contains an epoK gene that encodes epothilone epoxidase. If an inhibitor of this particular gene product is intended, then the article ---the---, instead of "a" should be used to describe epothilone epoxidase in the claims. On page 4, line 19 of the instant specification, the phrase "such as EpoK" is used to indicate that other epothilone epoxidase gene products are intended by the term. If this term, in fact, is meant to include other epothilone epoxidases, the nature is wholly unclear as there are no others described in the specification and/or the art. Clarification is required.

12. Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "acetylenic mechanism-based irreversible inhibitors" is unclear as to its metes and bounds. Are all acetylene compounds encompassed? What mechanisms must be inhibited? Clarification is required.

13. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "preferably" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See M.P.E.P. § 2173.05(d). Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-6 and 8 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods of making desoxyepothilones using fermentation processes in the presence of epothilone epoxidase inhibitors. To adequately describe the genus of methods using any epothilone epoxidase inhibitors, the products themselves must be adequately described. That is not the case here.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a single example of an epothilone epoxidase inhibitor useful in the claimed methods is described, metyrapone (see Example 4). While the specification describes, at length, procedures for assaying for inhibitors of epothilone epoxidase using a purified epoK gene product (pages 20-21) and while the specification proposes numerous compounds as inhibitors, such as P_{450} enzyme inhibitors, acetylenic mechanism-based inhibitors, etc., still only a single species of the inhibitors is demonstrated. No discussion of the structure of metyrapone and how that structure relates to inhibiting function is described in the specification. In fact, the structures of the numerous proposed inhibitors and classes of inhibitors do not appear to have structural features in common with metyrapone. Thus, having only a single representative species and no structure/function relationship of how that single species functions to inhibit epothilone epoxidase, the species cannot adequately describe the claimed genus.

15. Claims 7-11 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods of producing a desoxyepothilone in the presence of numerous inhibitors, none of which have been demonstrated, or are known, as epothilone epoxidase inhibitors. Thus, to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in

Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the art, the epoK gene product is described as a P_{450} epoxidase (see USPN 6,303,342, column 8) because it has been shown to act as an epoxidase and its sequence resembles that of P_{450} enzymes. P_{450} enzymes are "one of the largest superfamilies of enzyme proteins" that are "extremely diverse" (see Abstract of Werck-Reichhart *et al.* Cytochromes P450: a success story. Genome Biol. 2000 Epub 1(6) (internet publication)). The use of different substrates in their diverse reactions renders generic use of general P_{450} enzyme inhibitors highly unpredictable in the absence of other evidence, such as crystal structure information of the epoxidase. Moreover, even if by chance some of the proposed P_{450} enzyme inhibitors effectively inhibit the epoK gene product (epothilone epoxidase), such inhibitors must also be tested for effectiveness in the

claimed method since fermentation is affected in the presence of P_{450} inhibitors. While the specification describes little effect on *S. cellulosum* growth in Example 4, the data in Figure 2 clearly evidence a detrimental effect on growth (see 5 mM and 10 mM metyrapone traces), which effect is noted as a distinct possibility in the specification itself (see page 13). Thus, the ability to identify the named compounds as epothilone epoxidase inhibitors at concentrations that do not affect overall microorganism cell growth is highly unpredictable so as not to be enabled for the claimed methods.

Allowable Subject Matter

16. Claim 6, drawn to methods of making desoxyepothilone by fermentation in the presence of metyrapone is free of the prior art. No prior disclosure of treatment of epothilone-producing microorganisms with this compound is known. While the prior art teaches inactivating the epoK gene recombinantly to produce an epothilone PKS in the absence of an epoxidase function for production of useful epothilones C and D (see particularly USPN 6,303,342), no motivation for using epoxidase inhibitors instead of recombinantly producing this same effect can be found since recombinant means are easier, less detrimental to the overall growth of the host cell, and described so as be enabled in the prior art, unlike use of epoxidase inhibitors.

Conclusion

17. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kathl Ke

KMK
August 7, 2003